Prospective Multi-Center Evaluation of the Duration of Therapy for Thrombosis in Children

Published: 28-05-2018
Last updated: 13-04-2024

Specific Aim #1: To evaluate the efficacy and safety of shortened-duration (6 weeks total) versus conventional duration (3 months total) anticoagulation for first-episode, provoked, acute venous thrombosis among children in whom thrombus resolution/...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON46920

Source
ToetsingOnline

Brief title
The "Kids-DOTT" Trial

Condition

- Embolism and thrombosis

Synonym
pulmonary embolism, thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: All Children□s Hospital Johns Hopkins Medicine
Source(s) of monetary or material Support: All Children's Hospital Foundation

Intervention

Keyword: anticoagulation, children, duration, thrombosis

Outcome measures

Primary outcome

PRIMARY EFFICACY:

Risk of symptomatic recurrent VTE within 1 year

PRIMARY SAFETY:

Risk of clinically-relevant (i.e., major plus clinically-relevant non-major [CRNM]) bleeding within 3 months (maximum randomized duration of anticoagulation) plus 10 days

Based upon ISTH standardized definitions for pediatric trials [Mitchell et al., 2011], *Major bleeding* will be characterized by bleeding satisfying any one of the following criteria: 1) fatal; 2) clinically overt and associated with a decrease in hemoglobin of at least 2 g/dL in a 24 hour period; 3) clinically overt and for which blood product is administered; 4) retroperitoneal, pulmonary, or involving the central nervous system; 5) requiring surgical intervention in an operating suite. *CRNM bleeding* definition includes any bleeding that does not fulfill the above criteria but fulfills one of the following: 1) Bleeding requiring medical or surgical intervention to restore hemostasis; 2) Bleeding for which medical attention is sought.

Secondary outcome

SECONDARY SAFETY:

1) Major bleeding episode (defined as above)

2) Minor bleeding episode (defined as all clinically-evident bleeding episodes not meeting criteria for Major or CRNM bleeding, above) within the therapy period. Nosebleeds lasting * 15 minutes, bleeding from superficial lacerations, and bruising at points of minor trauma are all considered as expected events on anticoagulation, and accordingly will not be collected.

SECONDARY EFFICACY:

1) Risk of symptomatic recurrent VTE at 2 years

2) Risks of PTS at 1 year and 2 years

Study description

Background summary

The incidence of pediatric thrombosis is rising due to advancements in diagnostic modalities for thrombosis, the rise in intensive approaches toward the support of critically ill children, and the heightened survival of children with chronic illnesses. Over 90% of VTE in children are classified as *provoked* (non-spontaneous), meaning that they have been provoked by the presence or insertion of a central venous catheter, recent hospitalization, surgery, trauma, immobility, infection, dehydration, flare of autoimmune condition, oral contraceptive use, etc.
In both children and adults, the current standard of care, is for anticoagulation of 3-6 months duration for a first-episode VTE in individuals with few and/or transient pro-thrombotic risk factors, based upon adult trials.
A prolonged duration of anticoagulation is indicated in VTE patients with chronic potent prothrombotic conditions, in those with unprovoked events (i.e., spontaneous; no clinical risk factors identified), and in antiphospholipid antibody (APA) syndrome, given an increased risk of recurrent VTE in these groups.
In both children and adults, either unfractionated heparin or LMWH may be used during the initial (i.e., acute) therapy phase, while either LMWH or vitamin K antagonists may be used during the extended (i.e., subacute) therapy phase.
The question as to whether outcomes for 6 week vs. 6 month anticoagulation in

adult VTE may be equivalent has not been definitively answered in adults. In children shortening of the duration of anticoagulation would lessen frequent invasive monitoring by venipuncture in patients treated with VKA, decrease the number of invasive twicedaily subcutaneous injections in patients treated with LMWH and decrease bleeding risk. Nevertheless, the desire to decrease cost and bleeding risks by shortening the duration of anticoagulant therapy must be balanced by the need to minimize risk of recurrent thrombosis. Unfortunately, the relative risk of recurrent VTE for shortened anticoagulation in the pediatric setting is unknown. Since the rate of recurrent VTE in children treated with standard duration anticoagulation appears to be quite lower than that for adults treated similarly, it is expected that the absolute increase in risk of recurrent VTE (if any) engendered by shortened anticoagulation will be smaller than that in adults.
No large prospective, randomized, controlled trials on the optimal duration of anticoagulation for first episode VTE have been performed to date in children. The Kids-DOTT study will provide key evidence for the optimal duration of anticoagulant therapy for thrombosis in children.

Study objective

Specific Aim #1: To evaluate the efficacy and safety of shortened-duration (6 weeks total) versus conventional duration (3 months total) anticoagulation for first-episode, provoked, acute venous thrombosis among children in whom thrombus resolution/non-occlusion (i.e. established blood flow) is evident after the initial 6 weeks of anticoagulant therapy

Specific Aim #2: To determine whether outcomes of first-episode, provoked, acute venous thrombosis (specifically, with respect to recurrent VTE and PTS) among children treated with conventional-duration (3 months total) anticoagulation differ between those with and without thrombus resolution/non-occlusion at 6 weeks.

Specific Aim #3: To evaluate whether the effect of treatment duration on the risks of symptomatic recurrent VTE and clinically-relevant bleeding in children with first-episode, provoked, acute venous thrombosis differs between subgroups defined by type of sub-acute anticoagulant therapy in real-world clinical use (all prescribed clinically, with the exception of investigational dalteparin, which was prescribed under an investigator-held IND through December 2013).

Specific Aim #4: To establish a clinical trial-derived plasma and nucleic acids biorepository for future proteomic, genomic, and metabolomic investigations of predictors and modulators of VTE outcomes in children.

Study design

If the patients fulfills the in- and exclusioncriteria, the patient can be

included into the study. This means that after 6 weeks the radiological tests will be repeated.

If thrombosis is still there or the lupus anticoagulans remains positive, the patient stays on anticoagulant treatment for at least 6 weeks.
If radiological investigation does not show thrombosis anymore after 6 weeks and lupus anticoagulans is negative, the patient can be randomized to group A (stop anticoagulation) or group B (standard of care: totally 3 months of anticoagulation).

Parents and/or patients may give permission to take blood 6 weeks and 3 months after diagnosis for biobank.

Intervention

If radiological investigation does not show thrombosis anymore after 6 weeks and lupus anticoagulans is negative, the patient can be randomized to group A (stop anticoagulation) or group B (standard of care: totally 3 months of anticoagulation).

Study burden and risks

The shortened-duration anticoagulation (6 week arm) may incur an increased risk of recurrent VTE, but this risk is likely minimized by randomization to this arm only among patients who have no evidence of completely-occlusive thrombosis after 6 weeks of initial therapy. Furthermore, if an increased risk of recurrent VTE indeed exists in this carefully defined patient group, such risk may be offset by a decreased risk of bleeding potentially offered by abbreviated anticoagulation.

Contacts

Public
All Children□s Hospital Johns Hopkins Medicine

6th Ave S 501
St Petersburg FL 33701
US
Scientific
All Children□s Hospital Johns Hopkins Medicine

6th Ave S 501
St Petersburg FL 33701
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

(1) Children (birth to <21 years of age) with radiologically-confirmed acute venous thrombosis in the past 30 days;(2) In the opinion of the investigator, the venous thrombosis was a provoked (i.e., non-spontaneous) event (e.g.: hospitalization; Central venous catheterization; infection; dehydration; surgery; trauma; immobility; use of estrogen-containing oral contraceptive pills; flare of autoimmune/rheumatologic condition).

Exclusion criteria

(1) prior episode of VTE;;(2) presence or history of cancer;;(3) systemic lupus erythematosus;(4) known pulmonary embolism (PE), except when limited to peripheral cavitary lesions representing septic emboli; (N.B. imaging for PE should only have been based upon clinical signs/symptoms, and is not a study procedure or requirement);(5) Use of, or intent to use, thrombolytic therapy;(6) Patients with congenital cardiac disease involving a single or hypoplastic ventricle or otherwise requiring aintracardiac shunt;(7) Moderate/severe anticoagulant deficiency as defined by any one of the following:;a. protein C <20 IU/dL if patient is *3 months of age, or protein C below lower limit of detection if patient is <3 months of age;;b. antithrombin <30 IU/dL if patient is *3 months of age, or antithrombin below lower limit of detection if patient is <3 months of age;;c. protein S (free antigen or activity) <20 IU/dL.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	acenocoumarol
Generic name:	acenocoumarol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fraxiparin
Generic name:	nadroparin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Heparin Leo
Generic name:	unfractionated heparin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Marcoumar
Generic name:	Marcoumar
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-05-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-001776-21-NL
ClinicalTrials.gov	NCT00687882
CCMO	NL56060.078.17